

REMARKS

Claims 46-65 were pending in the present application. Claims 58 and 59 have been amended to correct minor typographical errors. Claim 65 has been amended to be dependent upon any of claims 46-53, 56, 58 and 63. Support for this amendment can be found in the specification, for example, at page 11, lines 10-13 and lines 23-24. No new matter has been added by these amendments. Upon entry of these amendments, claims 46-65 will remain pending in the present application.

Applicant respectfully requests that the amendment and remarks made herein be entered and fully considered.

The Rejection Under 35 U.S.C. § 103(a) Should be Withdrawn

Claims 46-57 and 63-65 have been rejected under 35 U.S.C. § 103(a) as being obvious over Kensil et al. (U.S. Patent No. 5,057,540; “Kensil”) and Allison et al. (U.S. Patent No. 4,772,466; “Allison”). Applicants respectfully disagree with the Examiner’s rejection and submit that the rejection should be withdrawn for the reasons discussed below.

The Examiner contends that Kensil teaches an immunogenic composition comprising an antigen and a saponin adjuvant. The Examiner notes that Kensil does not teach a non-ionic surfactant as an excipient.

The Examiner contends that Allison teaches vaccines comprising an antigen and a polyoxypropylene-polyoxyethylene polymer for immunization. The Examiner further contends that Allison teaches that non-ionic surfactants, including polysorbates, are useful in vaccine formulations as they increase the efficacy of the vaccine compositions and stabilize the emulsion when a suspension is formed.

The Examiner thus concludes that it would have been obvious to one having ordinary skill in the art at the time the invention was made to employ the excipient components taught by Allison in the immunogenic composition taught by Kensil. The Examiner alleges that one of ordinary skill in the art at the time the invention was made would have been motivated to do so because the teaching of Allison provides an obvious way to increase efficacy and stabilize the vaccine formulation of the claimed invention. The Examiner further alleges that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the

reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. M.P.E.P. § 2143. If any one of these criteria are not met, *prima facie* obviousness is not established, and Applicants are not required to show new or unanticipated results. *In re Grabiak*, 226 USPQ 870 (Fed. Cir. 1985).

Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art. “The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art.” *In re Kotzab*, 217 F.3d 1365, 1370, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000). See also *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). MPEP 2143.01.

Unexpected results may be used as evidence of nonobviousness. “A greater than expected result is an evidentiary factor pertinent to the legal conclusion of obviousness ... of the claims at issue.” *In re Corkill*, 711 F.2d 1496, 226 USPQ 1005 (Fed. Cir. 1985). See MPEP § 716.02(a).

With respect to the bases for the Examiner’s rejection, relating to the use of a non-ionic surfactant, Applicant respectfully disagrees and submits that the presently claimed invention is not obvious because the art cited by the Examiner provides no suggestion or motivation to use a non-ionic surfactant such as Polysorbate or Triton X-100 with a saponin adjuvant.

Kensil describes the use of substantially pure saponins as adjuvants. Immunologic compositions are also provided comprising a saponin adjuvant in combination with an antigen component. Kensil describes the use of saponins, optionally, with non-saponin adjuvants and/or inert carriers. See, e.g., Kensil, col. 7, lines 20-31 and col. 8, lines 7-11. There is no teaching, suggestion or motivation in Kensil to use compositions comprising saponins and non-ionic surfactants such as Polysorbate or Triton X-100 to enhance an immune response to an antigen in an individual. Thus, Kensil does not render obvious the presently claimed invention.

Allison does not remedy the deficiencies of Kensil. Allison describes vaccines comprising an antigen, a polyoxypropylene-polyoxyethylene block polymer, a glycol ether-

based surfactant, an immunostimulating glycopeptide, and optionally, a metabolizable non-toxic oil. Allison describes the emulsification of glycopeptides and an antigen using a polyoxypropylene-polyoxyethylene block polymer and a multiphase-stabilizing amount of a glycol ether-based non-toxic surfactant. See, e.g., Allison, col. 2, lines 23-34. A class of compounds described for use as a emulsifying or suspending agent is polyoxyethylene sorbitan monoesters, including polysorbate 80. See Allison, col. 5, lines 34-36 and col. 6, lines 46. Allison teaches that a glycol ether-based surfactant stabilizes the polyoxypropylene-polyoxyethylene block polymer which in turn increases the efficacy of an immunostimulating glycopeptide as an adjuvant. The Examiner seems to suggest that because Allison teaches that a non-ionic surfactant increases the efficacy of a specific adjuvant composition and stabilizes such a specific adjuvant composition, wherein the adjuvant composition is an emulsion comprising a polyoxypropylene-polyoxyethylene block polymer and a glycopeptide, a non-ionic surfactant would be useful for increasing the efficacy of any adjuvant including those where an adjuvant has not been shown to form an emulsion or need to be formulated as an emulsion to improve its activity. Allison teaches that glycol ether based surfactants help stabilize a polyoxypropylene-polyoxyethylene block polymer. The choice of surfactants to be used in the invention of Allison likely depends on the size of the polyoxyethylene moiety and the HLB value. See Allison col. 6, lines 7-9 and 25-28. Thus, the choice of a surfactant depends on the polyoxyethylene moiety used and what would be a compatible HLB value. The teachings of Allison do not suggest the general applicability of polysorbates for stabilizing compounds other than those comprising a polyoxypropylene-polyoxyethylene block polymer. Contrary to the Examiner's suggestion, Allison does not teach or suggest the desirability of using an emulsifying or suspending agent, such as a polysorbate, with compositions other than those comprising a polyoxypropylene-polyoxyethylene block polymer, much less those comprising a saponin adjuvant. Thus, Allison, whether alone or in combination with Kensil, does not render obvious the presently claimed invention. Accordingly, the references cited by the Examiner do not provide a *prima facie* case of obviousness.

Even assuming, *arguendo*, that Kensil and Allison could be properly combined, Applicants respectfully submit that unexpected results are provided. The present invention demonstrates that the combination of a saponin adjuvant and a polysorbate reduces the lytic effect of a saponin (see Example 1), improves the pain tolerance to saponin compositions (see Examples 5 and 6 and Figs. 3-5) and stabilizes compositions comprising a

saponin adjuvant, surprisingly without compromising the full adjuvant potency of the saponin (see the specification at page 4, lines 9-21 and Fig. 1A). These improved properties would not be expected by one of skill in the art and provide evidence of nonobviousness of the invention.

In view of the foregoing, Applicants respectfully assert that the rejection of the pending claims under 35 U.S.C. § 103(a) is in error and respectfully request that the rejection be withdrawn.

CONCLUSION

Applicants respectfully request that the present amendments and remarks be made of record in the instant application. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

Respectfully submitted,

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